"DEVELOPMENT OF MICROSPONGE FOR TOPICAL DELIVERY OF DEXIBUPROFEN"

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INTRODUCTION

Over recent years, non-steroidal anti-inflammatory drugs (NSAIDs) have been increasingly introduced as topical preparations for local treatment of musculoskeletal soft-tissue rheumatic conditions. Topical NSAIDs have several advantages over their systematically administered counterparts – they are simple to apply and deliver high drug concentrations locally into affected tissues, while producing limited systemic absorption; thus they have a greatly reduced propensity to elicit adverse systemic effects. By contrast, orally administered NSAIDs, which generate high systemic drug concentrations, are often poorly tolerated because of gastrointestinal or renal adverse effects. (McPherson, 2013:35-39)

The nonsteroidal anti-inflammatory drugs (NSAIDs) are used in fever, pain, and inflammation because these drugs possess antipyretic, analgesic, and anti-inflammatory properties. Clinically, they are useful in relieving pain in many conditions, ranging from menstrual and postoperative pain to arthritic pain. These drugs are well-known anti-inflammatory agents, and they exert their effects through the inhibition of prostaglandin synthesis by blocking the enzyme cyclooxygenase (COX). In the past few decades, there is a growing body of research on the use of NSAIDs in cancer treatment and prevention, whereas the relationship between chronic inflammation and cancer has long been discovered. (Wong, R.S., 2019: 1-10)

Dexibuprofen belonging to the class of (+)-(*S*)-2-(4-isobutylphenyl)-propionic acid, is a chiral 2-arylpropionic acid (2-APA) derivative non-steroidal anti-inflammatory drugs (NSAIDs) is a well-known and extensively used drug. It is the first choice of its own class "profens" due to the low incidence of unwanted side effects. Dexibuprofen has been tested and proved to be effective as an analgesic, anti-pyretic and anti-inflammatory after systemic administration. When administered as a topical preparation, Dexibuprofen has been shown to be an effective topical analgesic and anti-inflammatory for the relief of mild to moderate arthritic pain, mustratum corneumular pain, backache, sprains, strains, lumbago and fibrositis by virtue of percutaneous absorption. (Yoon, 2008:854-860)

Microparticles and nanoparticles have been increasingly investigated to achieve targeted and sustained release of drugs. Microsponges are porous, polymeric microspheres that are mostly used for prolonged topical administration. Microsponges are designed to deliver a pharmaceutically active ingredient efficiently at minimum dose and also to enhance stability, reduce side effects, and modify drug release profiles. (Amrutiya Netal, 2009: 402-9)

Potential Advantages of the Microsponge Drug Delivery System (MDS)

- Microcapsules cannot usually control the release rate of the active pharmaceutical ingredients (API). Once the wall is ruptured the API contained within the microcapsules will be released. Can the MDS can do it, is the question.

- Liposomes suffer from a lower pay load, difficult formulation, limited chemical stability, and microbial instability. Do the MDS have a wide range of chemical stability and are they easy to formulate?

- MDS have stability over a pH range of 1 – 11.
- Stable up to temperature 130°C.
- Pay load is up to 50 – 60%.
- Free flowing and cost effective.
- Microsponges are microscopic spheres capable of absorbing skin secretions, therefore, reducing oiliness and shine from the skin.

Properties of the Actives for the Entrapment into Microsponges

- It should be either fully miscible in a monomer or capable of being made miscible by the addition of a small amount of a water-immiscible solvent.
- It should be water immiscible or at most only slightly soluble.
- It should be inert to monomers and should not increase the viscosity of the mixture during formulation.
- It should be stable when in contact with the polymerization catalyst and under conditions of polymerization.
- The spherical structure of the microsponges should not collapse. (Kaity 2010: 283-90)

Microsponge's drug delivery system can be prepared in two ways, one-step process or by two-step process that is liquid-liquid suspension polymerization and quasi emulsion solvent diffusion techniques based that is based on physicochemical properties of drug to be loaded. (Charde, 2013:63-70)

1. Liquid-liquid suspension polymerization-

2. Quasi-emulsion solvent diffusion:-

The oral administration of dexibupfrofen have some disadvantages like, Upset stomach, nausea, vomiting, headache, diarrhea, constipation, dizziness, or drowsiness. The disadvantages of dexibuprofen drug may be overcome by loading the drug into topical microsponge.

So, present study is designed to develop a drug delivery system for localized action of drugs used in treatment of arthritis to the affected tissues for prolonged period and to avoid side effects in non-target organs. To achieve this, the drug loaded in microsponge were prepared for nonsteroidal anti- inflammatory drugs and further incorporated in topical gel formulation.

LITERATURE REVIEW

Mahajan A. *et al* (2011), was prepared and studied controlled release formulation of microsponge was prepared by using Eudragit RS100, pH independent release retardant polymer and PVA stabilizer and emulsifier microsponge were prepared by quasi emulsion solvent diffusion method by changing drug: polymer ratio (3:1,4:1,5:1) and process was optimized and concluded that microsponge prepared in this study are promising as being more useful than conventional formulation in therapy.

Jain V. *et al* (2010), was prepared and evaluated Paracetamol loaded Eudragit based microsponges using quasi emulsion solvent diffusion method. The formulations were subjected to in vitro release studies and the results were evaluated kinetically and statically. The in vitro release data showed a bi-phasic pattern with an initial burst effect. The colon specific tablets were prepared by compressing the microsponges followed by coating with pectine: hydroxy propyl methyl cellulose(HPMC) mixture. In vitro release studies exhibited that compression coated colon specific tablet formulations started releasing the drug at 6th hour corresponding to the arrival time at proximal colon.

Nokhodchi A. *et al* (2005), was prepared Benzoyl peroxide (BPO) microparticles for treatment of acne vulgaris. Benzoyl peroxide micro particles were prepared using an quasi emulsion solvent diffusion method. Microparticles were then incorporated into various formulations (creams, gels and lotions) for release studies. It was shown that the drug: polymer ratio, stirring rate, volume of the dispersed phase influenced the particle size and drug release behavior of the formed microsponges and that the presence of emulsifier was essential for microsponge formation. The release data showed that the highest release rate was obtained from lotions containing BPO micro particles and the lowest was obtained from cream formulations.

Maiti S. *et al* (2011), was prepared and evaluated microsponges by the double emulsification technique and subsequently dispersed in a carbopol gel base for controlled delivery of diclofenac sodium to the skin. Scanning electron microscopy revealed the porous, spherical nature of the microsponges. The microsponges prepared at the lowest drug/polymer ratio exhibited a comparatively slower drug permeation profile and were hence considered most suitable for controlled drug delivery application. FTIR spectroscopy and DSC analyses indicated the chemically stable, amorphous nature of the drug in these microsponges. The gel containing these optimized microsponges was comparable to that of a commercial gel formulation and did not show serious dermal reactions. Hence, the microsponge system obtained at the lowest drug/polymer ratio could be useful for controlled release of diclofenac sodium to the skin.

Shahin M. *et al* (2011), was prepared Jojoba oil-based emulgel formulations using different concentrations of various gelling agents, such as hydroxypropyl methylcellulose (HPMC) and Carbopol 934 P and combination of both. The prepared emulgels were evaluated for their stability after temperature cycle test, centrifugation and long-term shelf storage for 1 year at room temperature. The prepared emulgels exhibited non-Newtonian shear thinning behavior with little or no thixotropic. The in vitro release test showed variation in the extent of percent drug released. The drug release from the commercial preparation was lower than some of the prepared emulgel formulae.

Yadav V, *et al* (2017), was prepared by quasi-emulsion solvent diffusion method by using polymer eudragit S-100 and eudragit L-100. All the formulated microsponges were subjected for various evaluation parameters such as production yield, encapsulation efficiency, particle size analysis and *in vitro* drug release study. The optimised microsponge formulations were further formulated as gel formulation for topical delivery. Prepared gel was evaluated for physical parameters like pH, spreadability, viscosity, drug content and *in vitro* diffusion study and compared with the marketed formulation.

Pande V.V, et al (2015), was developed a topical formulation that releases the drug in controlled manner, reduce the side effects associated with topical drug delivery and improve product efficacy with aid of microsponges. Microsponges loaded with sertaconazole nitrate were prepared by using quasi emulsion solvent diffusion with five different proportions of the polymer (Eudragit RS 100). The developed microsponges were analyzed for particle size, production yield, entrapment efficiency and drug content. Scanning electron microscopic images of microsponges revealed that they are spherical in shape and contain pores. Pore structure analysis was done by using mercury intrusion porosimetry technique, which confirmed the porous nature of microsponges. Microsponges were then incorporated in to a 1% corbopol gel and evaluated for pH, drug content, texture profile analysis and in vitro drug release.

Buddhabhushan V., (2019), was prepared to retain dosage form on skin. Microsponge systems are non-irritating, non-mutagenic, non-allergenic and non-toxic. Microsponges was prepared for colon specific delivery and controlled release drug delivery system to improve patient compliance by providing site specific drug delivery system and prolonging dosage intervals. Microsponges are generally prepared by several methods i.e. Liquid-liquid suspension polymerization and quasi emulsion solvent diffusion method. The present review introduces Microsponge methodology along with its principle, characterization such as Particle size and its distribution, surface morphology, porosity, density, parameters and release mechanism and drugs incorporated in MDS.

Amritiya N, *et al* (2009), was developed and evaluates microsponge-based topical delivery system of mupirocin for sustained release and enhanced drug deposition in the skin. Microsponges containing mupirocin were prepared by an emulsion solvent diffusion method. The effect of formulation and process variables such as internal phase volume and stirring speed on the physical characteristics of microsponges were examined on optimized drug/polymer ratio by 3^2 factorial design. The optimized microsponges were incorporated into an emulgel base. *In vitro* drug release, *ex vivo* drug deposition, and *in vivo* antibacterial activity of mupirocin-loaded formulations were studied. Emulgels containing microsponges showed desired physical properties. Drug release through cellulose dialysis membrane showed diffusion-controlled release pattern and drug deposition studies using rat abdominal skin exhibited significant retention of active in skin from microsponge-based formulations by 24 h. The optimized formulations were observed stable and nonirritant to skin as demonstrated by Draize patch test. Microsponges-based emulgel formulations showed prolonged efficacy in mouse surgical wound model infected with *S. aureus*. Mupirocin was stable in topical emulgel formulations and showed enhanced retention in the skin indicating better potential of the delivery system for treatment of primary and secondary skin infections, such as impetigo, eczema, and atopic dermatitis.

Vijay Rajaram Mahajan, *et al,* (2019), was prepared emulgel of Dexibuprofen, a NSAID, using Carbapol 940 as a gelling agent. Clove oil and Mentha oil were used as penetration enhancers. The emulsion was prepared and it was added in gel base. The formulations were evaluated for rheological studies, spreading coefficient studies, bioadhesion strength, skin irritation studies, in vitro release, ex vivo release studies, anti-inflammatory activity and analgesic activity. Formulation showed comparable analgesic and anti-inflammatory activity when they compared with marketed diclofenac sodium gel.

P.K. Lakshmi, *et al,* (2011), was studied the therapeutic effectiveness of Ibuprofen by increasing its transdermal permeation, via solid dispersion incorporated in gel. 2-hydroxy propyl beta cyclodextrins (2-HPβ-CD) and β-cyclodextrin (β-CD) were used as carriers and carbopol 941 was the gelling agent. The optimized solid dispersion of ibuprofen was incorporated into gel and was compared with penetration enhancers. The formulations were analyzed for physiochemical parameter and in vitro drug release. In ex vivo studies, formulations gave drug release within 24h.

AIM AND OBJECTIVE

Aim- To develop microsponges for topical delivery of Dexibuprofen.

Objective-

- To prepare, optimize, characterize Microsponges system for Topical application System.
- To perform Preformulation studies of selected API.
- To prepare and evaluate drug loaded micropsonges hydrogel.
- To improve the efficacy, drug loading capacity and biocompatibility of drug by formulating in microsponge.
- Physicochemical, *in-vitro* and *in-vivo* evaluation of optimized formulation.
- To study stability of optimized formulation.

PLAN OF WORK

1. **Extensive Literature review**
2. **Selection and Collection of drug & excipients**

Selection of drug: drug will be selected based on following criteria:

I. Solubility of drug in water is less than 10 mg/ml.

II. The molecular weight of drug between 100 to 400 gm/mole.

III. The melting point of drug should be less than 250^0C.

Drug: Dexibuprofen

Selection of polymer: polymer will be selected from following:

Hyper crosslinked Polystyrenes, Cyclodextrins and its derivatives Copolymers like Poly (valerolactoneallylvalerolactone) and Poly(valerolactoneallylvalerolactoneoxepanedione) Ethyl cellulose, PVA etc.

Selection of Crosslinkers: Crosslinkers will be selected from following: Diphenyl carbonate, Diarylcarbonates, Diisocyanates, Pyromellitic anhydride, Carbonyldiimidazoles, Epichloridrine, Glutarldehyde, Carboxylic acid dianhydrides, Dichloromethane etc.

Selection of apolar solvent: solvent will be selected from following: Ethanol, Dimethyl acetamide, Dimethyl formamide, Dimethyl sulfoxide, etc.

3. **Experimental work**

A. Preformulation studies:

- Procurement of drug samples and excipients
- Organoleptic properties
- Solubility analysis
- Melting point
- Partition coefficient
- UV spectral analysis
- FT-IR spectral analysis
- Differential Scanning Calorimetry (DSC)
- X-Ray Diffraction (XRD) analysis
- Drug excipients compatibility Study

Formulation development and preparation of microsponge

Microsponges will be prepared by using following methods:

- Emulsion solvent diffusion method

- Hyper cross linked β cyclodextrins
- Ultra sound assisted method

Preparation of microsponges Hydrogel

Nanosponges Hydrogel will be prepared by using suitable gelling agent e.g. Carbopol, HPMC, HEC etc. with suitable penetration enhancer like propylene glycol etc.

Optimization of drug-loaded microsponge & microsponge hydrogel

Evaluation of drug-loaded microsponge

- Particle Size and Zeta Potential measurement
- Surface morphology by Scanning Electron Microscopy
- Entrapment Efficiency
- Physical parameters
- FT-IR
- XRD
- Transmission Electron Microscopy(TEM)

4. Evaluation of drug-loaded microsponge Hydrogel

- Homogeneity
- Drug content
- Viscosity
- pH
- Spreadability

***In Vitro* drug release study**

***In Vivo* studies**

In vivo studies will be conducted using guinea pig or albino/wistar rats.

Skin irritation studies

Stability Studies as per ICH guideline

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